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Asymmetric Organocatalysis in Continuous Flow: Opportunities for Impacting Industrial Catalysis

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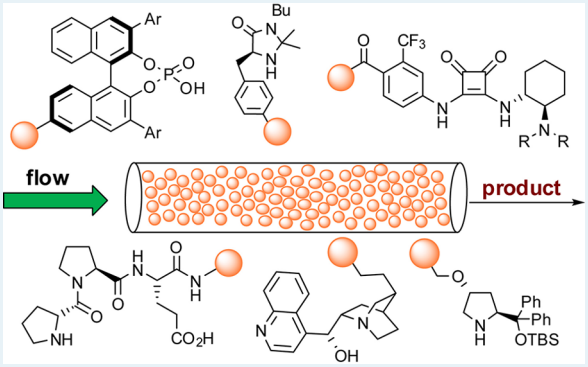
ABSTRACT: The review highlights the different advantages associated with organocatalytic transformations performed in continuous-flow systems and presents the reactions which have been successfully achieved to date. Particular focus is placed on the comparison between batch and flow applications in order to show the advantages and disadvantages and to demonstrate the great potential for applying organocatalysis as well as combined organo and photoredox catalyzed reactions in continuous flow.



KEYWORDS: *organocatalysis, photoredox catalysis, heterogeneous catalysis, immobilization, microreactor*

1. INTRODUCTION

Organocatalyzed reactions in which organic molecules catalyze single or multiple chemical transformations have evolved into a new field of research over the last years.[1−4] Although the field of organocatalyzed reactions is fairly new, it has experienced a quick and fascinating development in a short period of time, offering now a complementary approach to metal and biocatalyzed reactions. Nowadays, organocatalyzed reactions provide an alternative to enzyme- and metal-catalyzed reactions for creating complexity from simple starting materials in a convenient manner. Organocatalytic reactions were found to be an efficient synthetic tool for creating various new carbon−carbon and carbon−heteroatom bonds in the synthesis of a wide range of achiral and chiral acyclic as well as cyclic derivatives.

The benefits of organocatalytic reactions include the use of inexpensive and readily available organic compounds as catalysts, as well as increased synthetic efficiency as no metal traces have to be removed at the end of the process. Furthermore, these reactions are compatible with many different functional groups and provide in the case of asymmetric reactions high enantioselectivities for a variety of substrates. Overall, organocatalysis has become a valuable synthetic tool in the hands of organic chemists. Regarding the disadvantages of the organocatalyzed reactions, the relatively high catalyst loading (often 10−20 mol %) and the excess of one of the reagents constitute two main drawbacks. In addition, the common utilization of chlorinated solvents, the cumbersome product purification by column chromatography, and the need for catalyst recovery and reuse call for the design of more flexible and sustainable strategies in organocatalyzed reactions. To date, most of the experiments in the area of organocatalyzed reactions are carried out in batch mode on a laboratory scale. The scale-up of organocatalyzed reactions could bring additional benefits and prompt the application of such transformations in the industry. In recent years, continuous-flow technology has attracted the attention of the scientific community, and the development of convenient reaction systems is being actively pursued.[5−8] Continuous-flow processes are of great interest to the chemical industry. Continuous-flow transformations in microreactor technologies have several advantages over conventional batch synthesis as these processes feature the following: (i) large surface to volume ratios and enhanced mixing quality; (ii) superior mass and heat transfer and, hence, improved operational safety; (iii) good real-time reaction monitoring by incorporating inline analytical devices, allowing fast reaction screening and optimization; (iv) improved scalability. To date, continuous-flow microreactors have found various applications in standard transformations. Although the potential of carrying out asymmetric organocatalytic reactions in continuous flow was recognized at the end of 2000 by Lectka and co-workers (vide infra),[9,10] examples regarding the use of enantioselective organocatalyzed reactions in continuous flow are still scarce,[11−14] and the field of continuous-flow asymmetric organocatalyzed reactions is still in its infancy. The present review gives an overview of asymmetric organocatalyzed transformations performed in continuous flow and is organized by the type of reactions carried out in homogeneous and heterogeneous fashion, respectively. To facilitate a better understanding of the topic and various concepts applied, a

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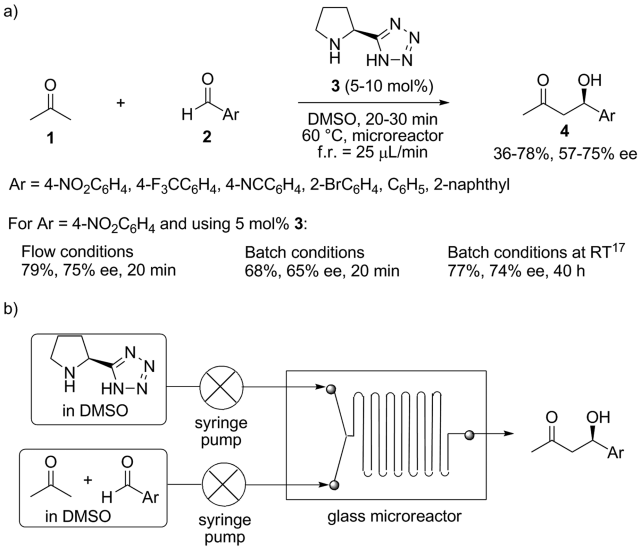
simple schematic representation of the continuous-flow experimental setup employed in these processes is also given.

2. HOMOGENEOUS REACTIONS

2.1. Aldol Reactions. The aldol reaction is one of the most widely used transformations for the efficient construction of C−C bonds.[15] The aldol reaction can be performed with a broad range of catalysts including conventional metal, organo- and biocatalysts as well as supported analogous catalysts. The aldol reaction plays an important role not only in the synthesis of simple β-hydroxy carbonyl compounds but also as a key step in the construction of structurally complex molecules. Among the organocatalysts employed, proline and proline derivatives are the most commonly used ones. Recently, the feasibility of performing organocatalyzed aldol reactions in continuous flow, increasing their efficiency by accelerating the reaction, and use of low catalyst loadings has attracted attention and was explored by different research groups in homogeneous and heterogeneous manner. In 2009, Odedra and Seeberger reported the 5-(pyrrolidin-2-yl)tetrazole-catalyzed aldol reaction in a continuous-flow reactor (Scheme 1).[16] The reaction of

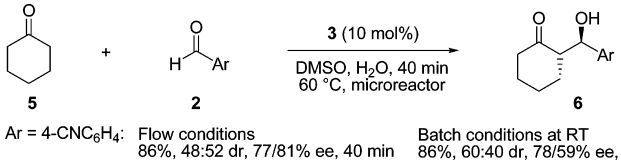
Scheme 1. (a) Proline-Derived Tetrazole Catalyzed Aldol Reaction in Continuous Flow; (b) Schematic Representation of the Experimental Setup for Continuous-Flow Aldol Reaction in a Glass Microreactor



acetone (**1**) with various aromatic aldehydes **2** proceeded quickly at 60 °C in a 1:1 DMSO/acetone mixture in a glass microreactor (V = 1 mL heated retention unit) to provide the corresponding products **4** in good yields and selectivities. In the case of 4-nitrobenzaldehyde (Ar = 4-$NO_2C_6H_4$), the reaction in flow at 60 °C provides the product with a higher yield and enantioselectivity (79%, 75% ee) compared with the same reaction performed in batch at 60 °C (68%, 65% ee) (Scheme 1a). Notably, the results obtained for the reaction performed in flow at 60 °C (Ar = 4-$NO_2C_6H_4$) compare well with the results obtained for the reaction at room temperature in batch (79% 75% ee vs 77%, 74% ee).[16−18] Comparable results were obtained in a glass chip reactor (75%, 76% ee, V = 250 μL), whereas the use of a tube reactor resulted in lower yield and selectivity (71%, 65%, V = 4 mL).

The reaction was also extended to cyclic ketones and the product **6** of the reaction between 4-cyanobenzaldehyde (Ar = 4-CNC_6H_4), and cyclohexanone (**5**) was obtained in 86% yield as a 1:1 mixture of diastereomers with 77 and 81% ee for the *syn* and *anti* isomers respectively (Scheme 2). At room

Scheme 2. Continuous-Flow Aldol Reaction with Cyclohexanone



temperature in batch, the same reaction requires 13.5 times longer reaction time and provides the product as a 1.5:1 mixture of diastereomers with 78 and 59% ee for the *syn* and *anti* isomers, respectively.

2.2. Michael Reaction. Michael reactions are widely applied in the laboratories for the construction of C−C and C-heteroatom bonds.[19] In the area of asymmetric Michael addition in continuous flow, Luisi and co-workers reported the homogeneous Michael addition of cyclohexanone (**5**) to nitroolefins **7** to yield products **8** with moderate to good levels of enantioselectivity (Scheme 3).[20]

2.3. Mannich Reaction. The Mannich reaction is another transformation of great importance in organocatalysis due to the usefulness of the gained products and its application in the synthesis of biologically active compounds. A first example for an organocatalyzed Mannich reaction performed under continuous-flow conditions was described by Odedra and Seeberger (Scheme 4).[16] By applying the same system setup as in the case of aldol reaction (see Scheme 1b), the addition of cyclohexanone (**5**) to *N*-PMP protected α-imino ethyl glyoxylate (**9**) was completed within 10 min, and the β-amino ketone product **10** was delivered in 91% yield and 95% ee.

2.4. Asymmetric Reduction. In 2012, Rueping and co-workers described the catalytic asymmetric transfer hydrogenation of a wide range of cyclic imines under continuous-flow conditions.[21] An inline ReactIR flow cell was used to monitor the reactions and adjust the reaction parameters until optimum conditions were found. For example, the transfer hydrogenation of quinolines **11** was more efficient when carried out in a microreactor compared to the reaction under batch conditions (Scheme 5). In situ ReactIR monitoring allowed recording of a reaction temperature profile for the determination of the optimum reaction temperature (Scheme 6a). Further optimization of the catalyst loading and residence time provided a set of optimum conditions for the reaction. Under the optimized conditions, a series of 2-substituted quinolines **11** were reduced in the presence of catalysts **14a**, and the corresponding tetrahydroquinolines **13** were obtained with excellent yields and enantioselectivities (91−97%, 94−99% ee). The generality and applicability of this protocol was proven in the reduction of further substrate classes like benzoxazines, quinoxalines, and 3*H*-indoles. In all cases, the final products were obtained with good to excellent enantioselectivities. In the case of quinoxalines, phosphoric acid **14b** was applied as catalyst. Chiral tetrahydroquinolines were also obtained starting from 2-aminochalcones by a photocyclization−Brønsted acid-catalyzed transfer hydrogenation cascade reaction in a

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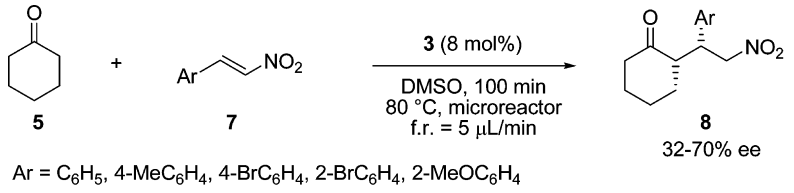
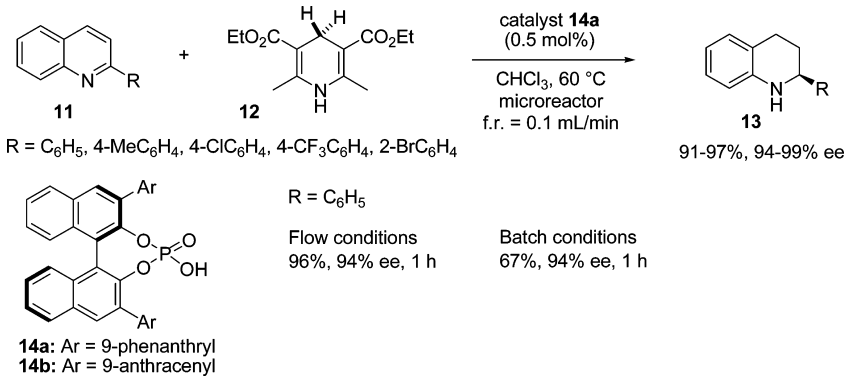
Scheme 3. Continuous-Flow Michael Addition Reactions

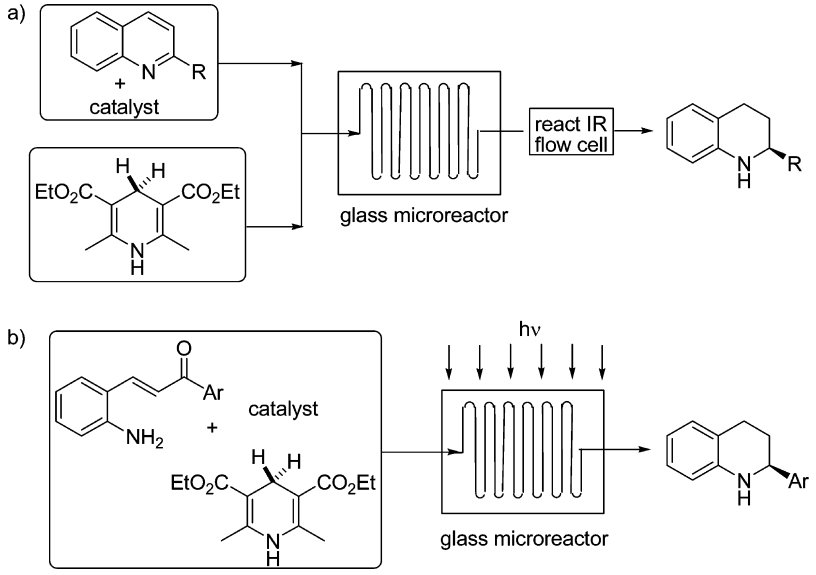


Scheme 4. Continuous-Flow Organocatalyzed Mannich Reaction

Scheme 5. Continuous-Flow Asymmetric Transfer Hydrogenation



Scheme 6. Schematic Representation of the Experimental Setup for Continuous Flow: (a) Asymmetric Transfer Hydrogenation; B) Photocyclization−Asymmetric Transfer Hydrogenation



continuous-flow microreactor system which was irradiated with a high-pressure mercury lamp (Scheme 6b).[22,23]

2.5. Enantioselective α-Alkylation of Aldehydes. Organic dyes are convenient photoredox catalysts due to their availability, low cost, and easy handling. Furthermore, like all organocatalyzed reactions, transformations using organic dyes as photoredox catalysts do not need post processing of the final product to remove traces of metals. Organic dyes have been successfully applied in several photoredox reactions;[24,25] however, their application in continuous-flow processes is in

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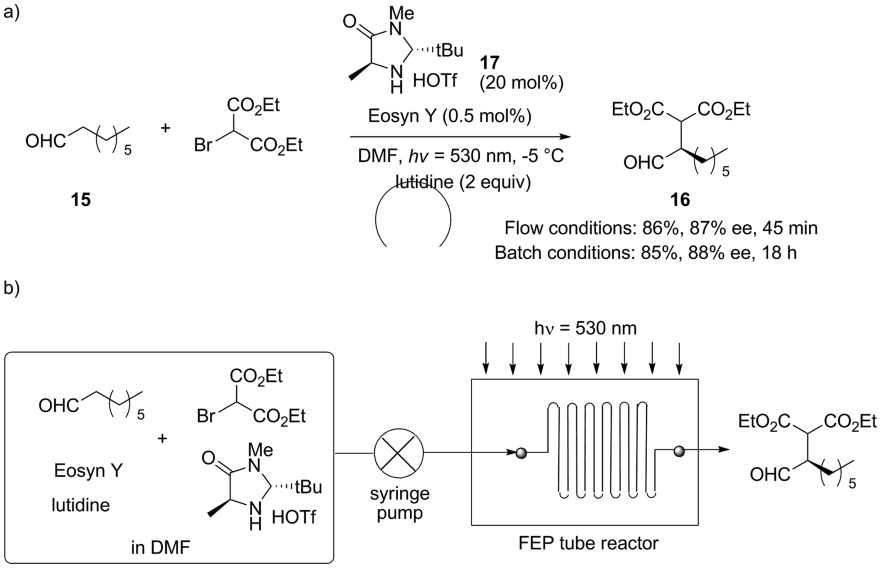
Scheme 7. (a) Visible-Light Continuous-Flow Enantioselective A-Alkylation of Octanal; b) Schematic Representation of the Experimental Setup for the Continuous-Flow Enantioselective A-Alkylation



progress. To date, one single example regarding the combination of an organic dye with a chiral organocatalyst has been reported. Neumann and Zeitler described the combination of Eosin Y as organophotoredox catalyst with imidazolidinone **17** as chiral organocatalysts for the enantioselective α-alkylation of *n*-octanal with bromomalonate using a microphotoreactor and green LEDs (Scheme 7).[26,27] In 45 min, the corresponding chiral α-alkylated aldehyde **16** was obtained in 86% yield and 87% ee. For the reaction in batch, 18 h where necessary in order to obtain similar results (Scheme 7).

3. HETEROGENEOUS REACTIONS

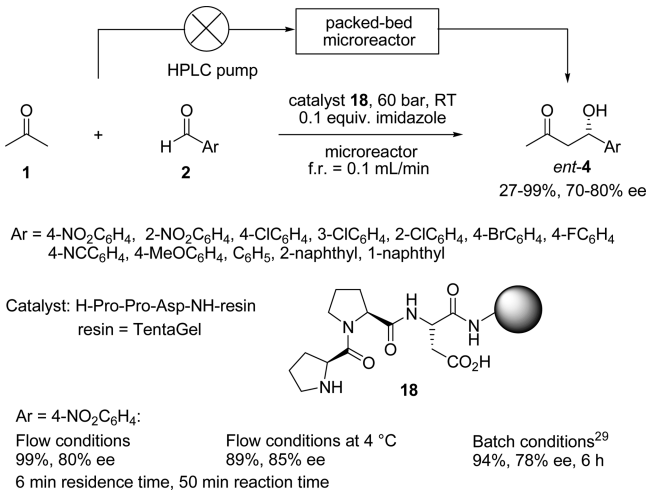
3.1. Aldol Reaction. The aldol reaction was performed also under heterogeneous conditions in continuous flow by employing various supported organocatalysts. A solid-supported peptide (H-Pro-Pro-Asp-NH-TentaGel) **18** was applied by Fülöp and co-workers in the continuous-flow aldol reaction between acetone (**1**) and various aromatic aldehydes **2** to give the corresponding β-hydroxyketones *ent*-**4** with good enantioselectivities in short reaction times (Scheme 8).[28] For example, in the case of 4-nitrobenzaldehyde (Ar = 4-$NO_2C_6H_4$), the product of the reaction with acetone in flow was obtained with high yield and enantioselectivity within considerably shorter reaction time when compared to the batch process.[28,29] A packed-bed microreactor was used in this study, and the catalyst activity was preserved even after 17 h of continuous use. By running the reaction for 80 h, a turnover number (TON) of 710 was estimated for the immobilized catalyst (TON batch = 472[29]).

A silica-supported 5-(pyrrolidin-2-yl)tetrazole catalyst **19** for the aldol reaction between cyclohexanone (**5**) and various aromatic aldehydes **2** under continuous-flow conditions was described by the groups of Cavazzini and Massi (Scheme 9).[30] Performing the reactions in toluene at 50 °C in a packed-bed microreactor afforded the desired products **6** as a mixture of two diastereomers (2:1 to 3:1 *anti* to *syn*) with 68−82% ee for the *anti* diastereomer.

The same groups described the application of covalently and noncovalently silica supported proline and proline-derived organocatalysts **20** and **21** for the aldol reaction between cyclohexanone (**5**) and 4-nitrobenzaldehyde (Ar = 4-$NO_2C_6H_4$) under batch and continuous-flow conditions (Scheme 10a).[31] Better results were observed with the covalently silica supported proline catalyst **21** under flow conditions. In this case, an additional cartridge packed with triamine-functionalized silica was used to remove the unreacted aldehyde from the reaction mixture (Scheme 10b). Furthermore, this transformation was investigated by reaction-progress kinetic analysis (RPKA) and nonlinear chromatography in order to determine the optimal operating parameters. For this purpose a 2D instrumental arrangement was devised to enable online flow-injection and flow reaction analysis.[32]

Sels and co-workers described also the application of a chiral noncovalently immobilized diamino catalyst **24** in an aldol reaction in a continuous-flow system (Scheme 11).[33] A shorter reaction time and slightly better diastereo- and enantioselectivity (3:1 vs 5:2 dr and 97 vs 94% ee) was observed when the reaction between 2-butanone (**22**) and 4-(trifluoromethyl)-

Scheme 8. Continuous-Flow Aldol Reaction in a Packed-Bed Microreactor with a Solid-Supported Peptide as Catalyst



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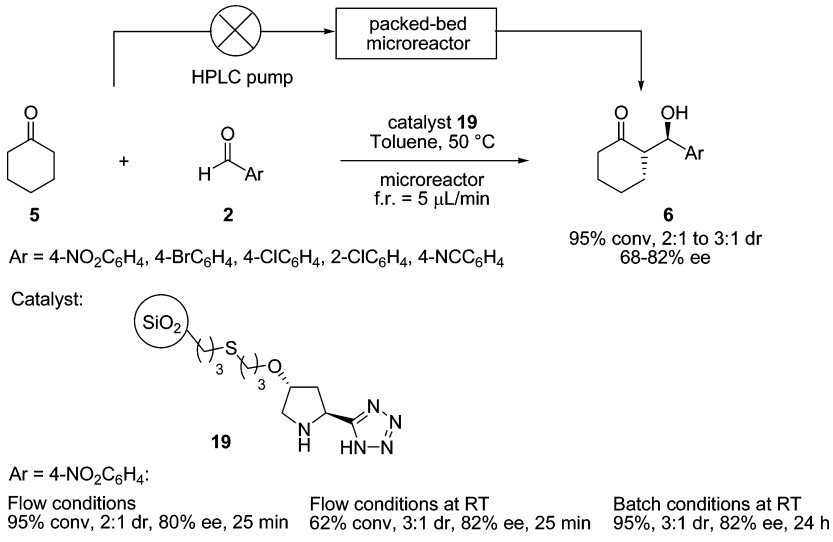
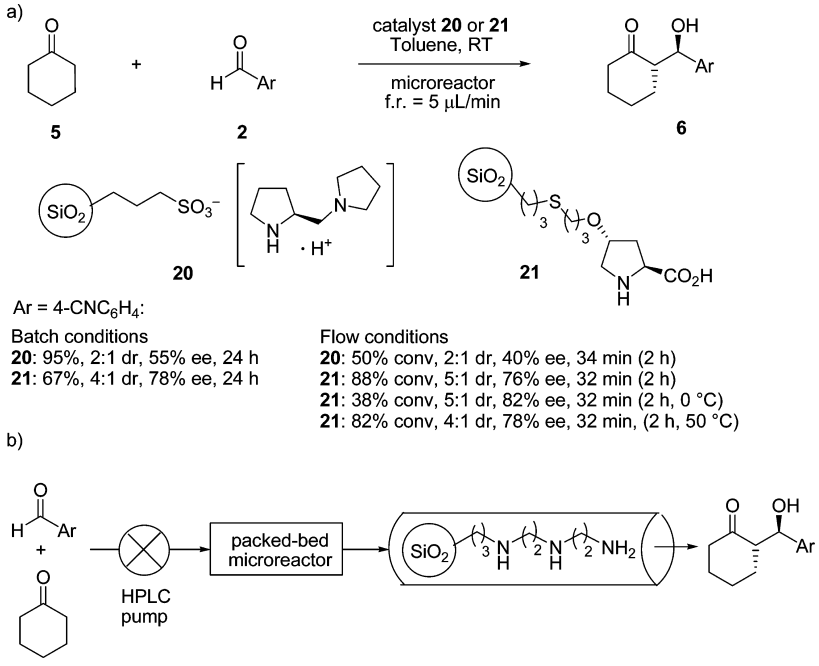
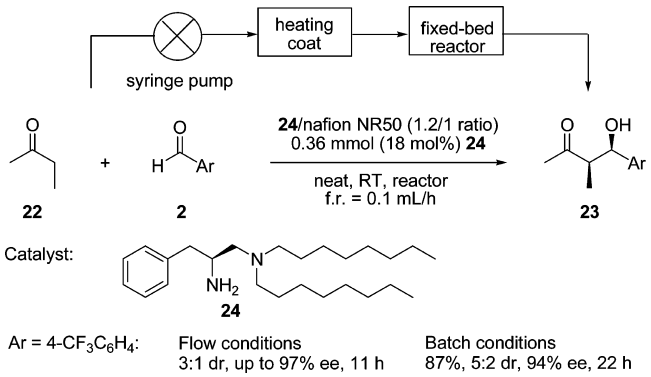
Scheme 9. Continuous-Flow Aldol Reaction with a Silica-Supported 5-(Pyrrolidin-2-yl)tetrazole Catalyst



Scheme 10. a) Continuous-Flow Aldol Reaction with Covalently and Non-Covalently Silica Supported Organocatalysts; b) Schematic Representation of the Experimental Setup



Scheme 11. Continuous-Flow Aldol Reaction with a Non-Covalently Immobilized Diamine Catalyst



benzaldehyde (Ar = 4-$CF_3C_6H_4$) was performed in flow with the chiral primary amino acid derived diamine **24** immobilized on sulfonated fluoropolymer nafion R NR50 as acid support.

Pericàs and co-workers described a polystyrene immobilized proline derivative for the asymmetric aldol reaction in flow (Scheme 12).[34] Excellent diastereo- and enantioselectivities for *β*-hydroxyketone products **6** were observed when polystyrene supported catalyst **25** was applied in the continuous-flow aldol reaction (96:4 to 97:3 dr and 95−98% ee) with a residence time of 26 min. Compared to the batch process which requires 10 mol % of catalyst loading, for the reaction in flow, the catalyst loading could be reduced to 1.6%.

3.2. Michael Reactions. In 2006, Hodge and co-workers described the first organocatalyzed Michael reaction in flow (Scheme 13).[35] By applying a fluid bed reactor and a polymer-supported cinchonidine **29** as organocatalyst (Scheme 14), the

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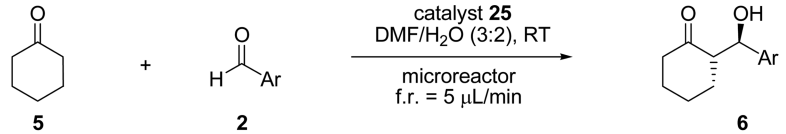
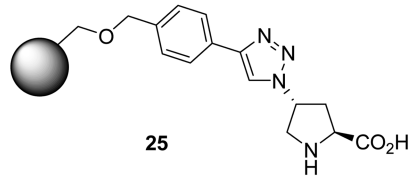
Scheme 12. Continuous-Flow Aldol Reaction with a Polystyrene Immobilized Proline Catalyst



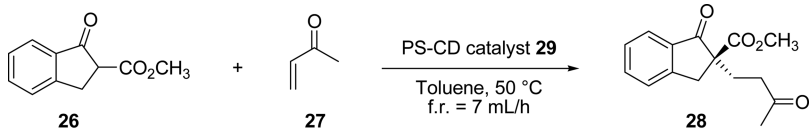
Catalyst:



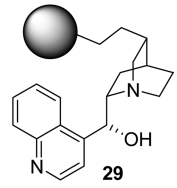
	Flow conditions[a]	Batch conditions[a]
Ar = 4-$NO_2C_6H_4$:	86%, 96:4 dr, 96% ee	99%, 97:3 dr, 98% ee, 16 h
Ar = 4-$F_3CC_6H_4$:	56%, 97:3 dr, 97% ee	97%, 97:3 dr, 99% ee, 16 h
Ar = 4-$MeO_2CC_6H_4$:	57%, 97:3 dr, 98% ee	97%, 97:3 dr, 99% ee, 20 h
Ar = 4-NCC_6H_4:	71%, 97:3 dr, 95% ee	99%, 96:4 dr, 94% ee, 13 h
	26 min residence time, 8 h reaction time	

[a]Conversion is indicated.

Scheme 13. Continuous-Flow Michael Addition with a Polymer-Supported Cinchonidine Catalyst



PS-CD catalyst:
polymer-supported cinchonidine catalyst

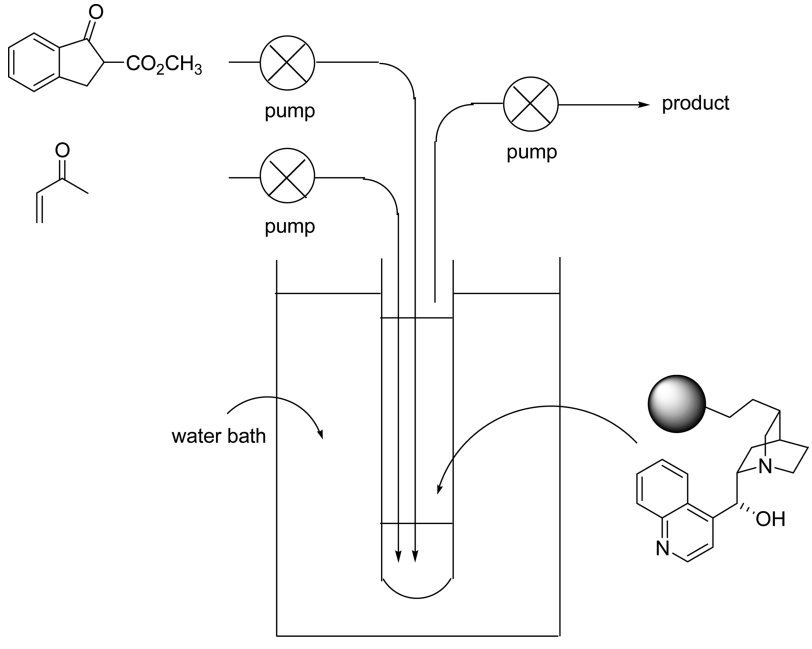


Flow conditions
97%, 51% ee
6 h residence time, 24 h reaction time

Batch conditions
98%, 47% ee, 24 h
[a] with cinchonidine as catalyst

Batch conditions[a]
91%, 53% ee, 3 h

Scheme 14. Schematic Representation of the Experimental Setup for Continuous-Flow Michael Addition According to Hodge



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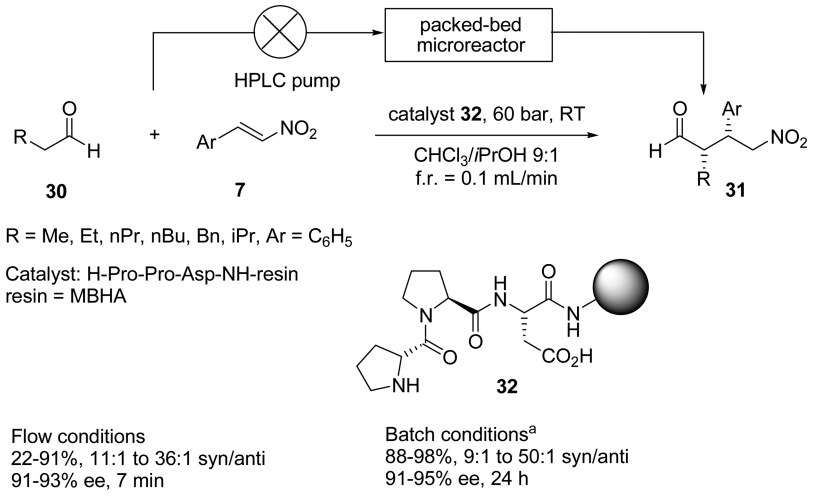
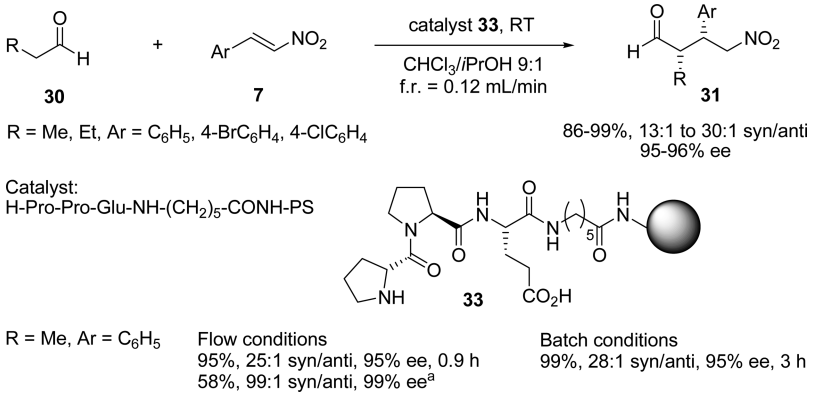
Scheme 15. Continuous-Flow Michael Addition with a Solid-Supported Peptide Catalyst



[a]The reactions in batch were performed with H-Pro-Pro-Asp-NH_2 as catalyst.

Scheme 16. Continuous-Flow Michael Addition with an Immobilized Peptide Catalyst



[a]After recrystallization.

product **28** of the 1,4-addition of methyl 1-oxoindan-2-carboxylate (**26**) to methyl, vinyl ketone (**27**) was obtained in 97% yield and 51% ee. This result compares well with the results obtained under batch conditions with the same polymer-supported cinchonidine **29** (98%, 47% ee) as well as with cinchonidine itself (91%, 53% ee) as catalysts. The reagents were pumped at the bottom of the tube which was filled with the catalyst bed and allowed to pass over the catalyst to the top of the tube from where the product was finally collected (Scheme 14). The reaction tube was placed in a water bath in order to ensure the desired temperature for the reaction.

More recently, solid-supported peptides have been applied as catalysts in the Michael addition of aldehydes to nitroolefins in continuous-flow processes by Fülöp and co-workers (Scheme 15).[36] With H-Pro-Pro-Asp-NH-resin (resin = MBHA) **32** as catalyst, a series of linear as well as α-branched aliphatic aldehydes **30** reacted with nitrostyrene (Ar = C_6H_5) to provide the corresponding γ-nitroaldehydes **31** in moderate to high yields (22−91%) and very high diastereo- and enantioselectivities (11:1 to 36:1 dr and 91−93% ee). In terms of selectivity, the results obtained in the continuous-flow process compare well with the batch process performed with the free peptide H-Pro-Pro-Asp-NH_2 as catalyst. The lower yields obtained in the continuous-flow process are due to the short residence time of 7 min applied thereby, whereby the batch transformations were performed for 24 h.

With immobilized H-Pro-Pro-Glu-NH_2 **33** as catalyst (H-Pro-Pro-Glu-NH-$(CH_2)_5$CONH-PS, PS = polystyrene), the addition of propanal and butanal to aromatic nitroolefins **7** was investigated by Arakawa and Wennemers (Scheme 16).[37] Notably, several different reactions (six different runs resulting in 351 mmol products) were performed on the same packed column (0.8 mmol immobilized catalyst) without affecting the activity of the catalyst. For more than 430 turnovers, the properties of the immobilized catalyst are comparable with the activity and selectivity of the fresh catalyst. A slight decrease in the catalytic activity was observed in the subsequent run; nevertheless, the catalytic activity can be restored by simply washing with an amine base solution and the catalyst can be employed in further reactions.

A polystyrene supported bifunctional chiral squaramide organocatalyst **36** was described by Pericàs and co-workers for the Michael addition of 2-hydroxy-1,4-naphtoquinone (**34**) to nitroolefins **7** under batch and continuous-flow conditions (Scheme 17).[38] High yields and excellent enantioselectivities were observed for various nitroalkenes **7** bearing electron-donating or -withdrawing substituents when the reactions were performed in batch (Scheme 17a). With this particular catalyst,

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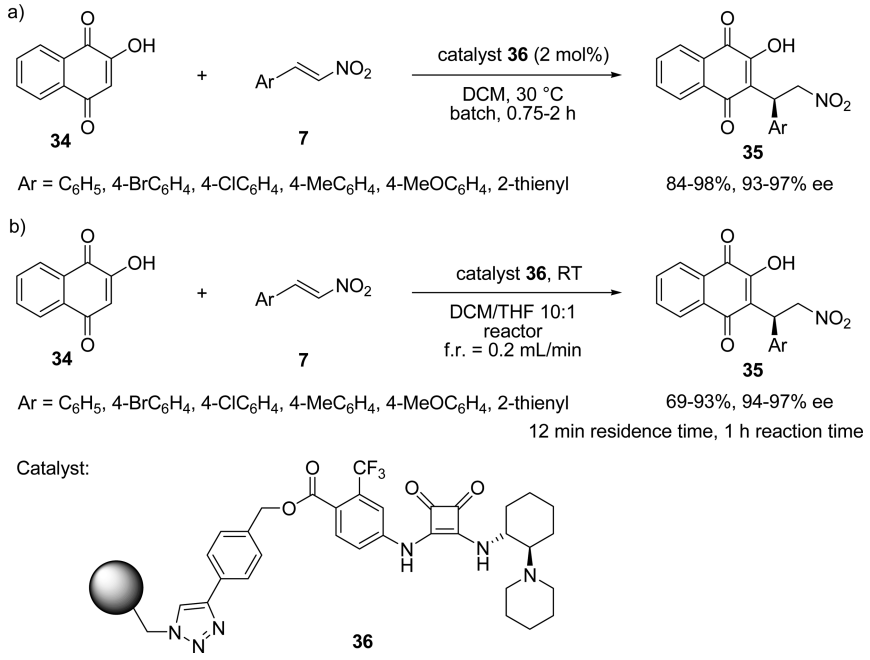
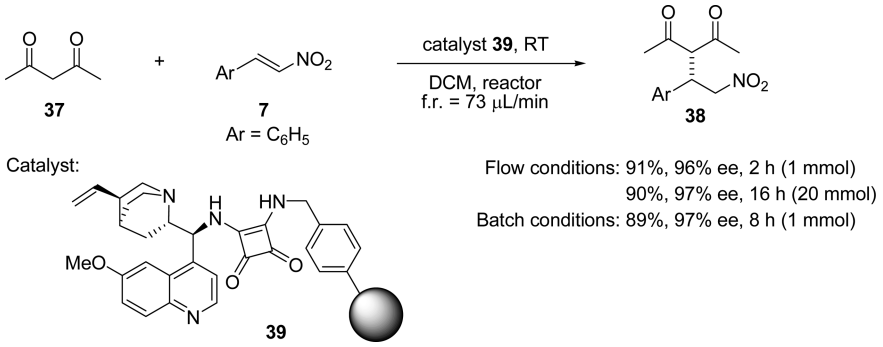
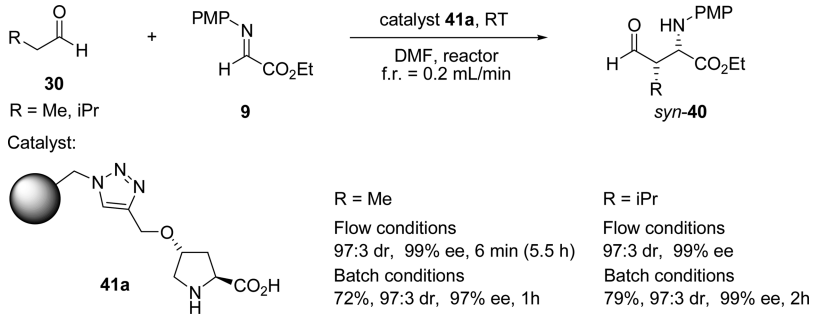
Scheme 17. Michael Addition with an Immobilized Bifunctional Chiral Squaramide Catalyst under a) Batch and b) Continuous-Flow Conditions



Scheme 18. Continuous-Flow Michael Addition with an Immobilized Bifunctional Chiral Squaramide Organocatalyst



Scheme 19. Continuous-Flow Organocatalyzed Mannich Reaction with Immobilized Hydroxyproline As Catalyst



the batch reactions were fast and required less than 2 h for completion. Comparable results were obtained for a variety of aromatic nitroolefins under continuous-flow conditions with a residence time of 12 min and 1 h reaction time (Scheme 17b). Only in the case of thienyl derived nitroolefin a lower yield (69% vs 90%) was obtained when the reaction was performed in flow. Notably, the reactions with different nitroolefin substrates were all performed on the same packed-bed reactor which was simply washed with a DCM/THF 10:1 mixture before a new reaction was started. Furthermore, for nitrostyrene as Michael acceptor, 6.6 g (75%) of the corresponding product were obtained with excellent enantioselectivity (96% ee) when the reaction was performed under continuous-flow conditions.

Kardos and Soós applied a polystyrene immobilized bifunctional chiral squaramide organocatalyst **39** in the continuous-flow addition of acetylacetone (**37**) to nitrostyrene (Ar = C_6H_5) (Scheme 18).[39] The reaction could be successfully

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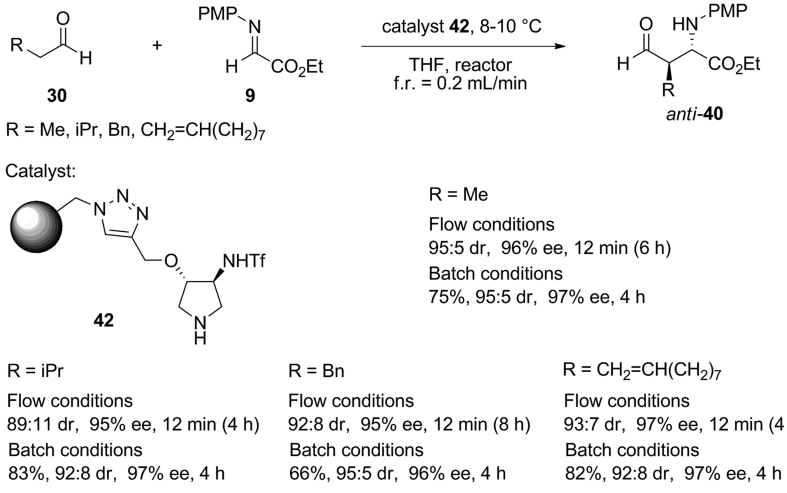
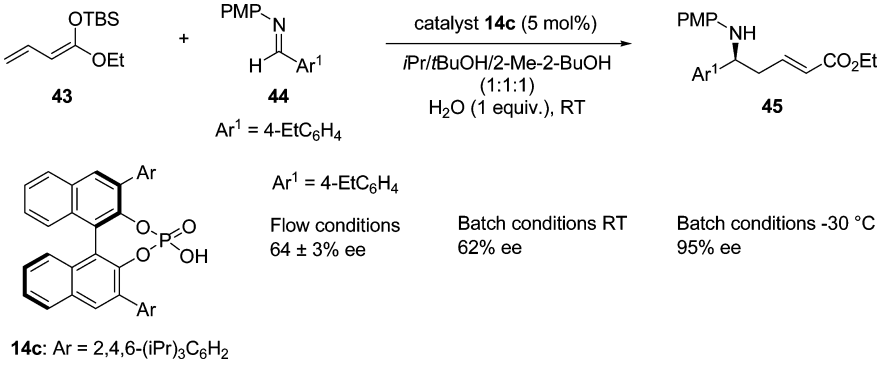
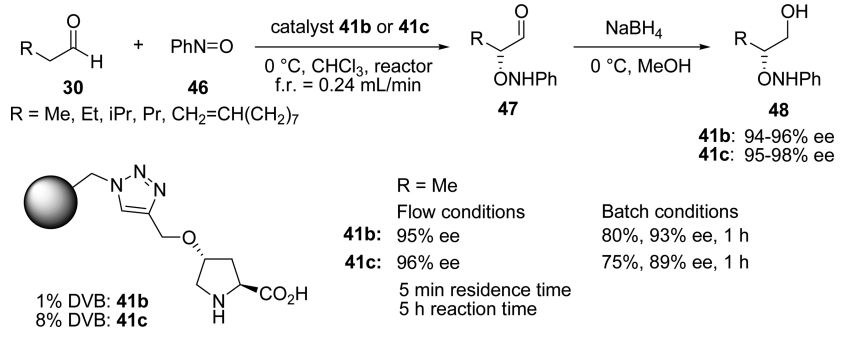
Scheme 20. Continuous-Flow Organocatalyzed Mannich Reaction with an Immobilized Pyrrolidine-Based Catalyst



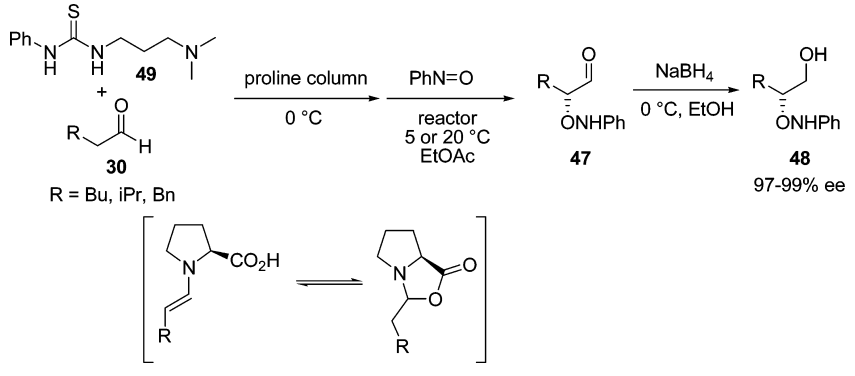
Scheme 21. Vinylogous Mannich Reaction in Continuous Flow



Scheme 22. Continuous-Flow α-Aminoxylation of Aldehydes



Scheme 23. Continuous-Flow α-Aminoxylation of Aldehydes with Proline



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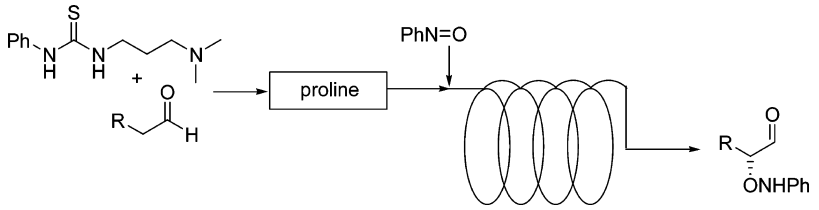
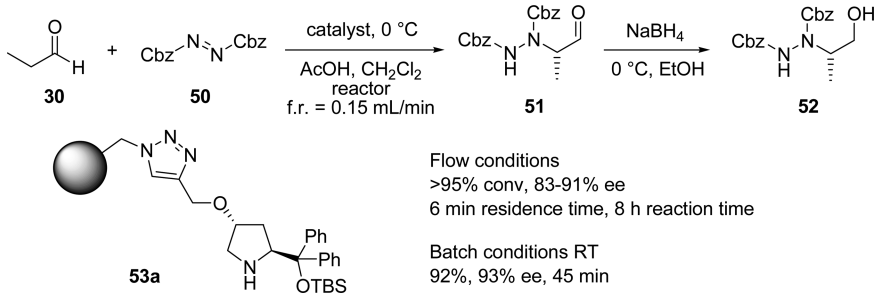
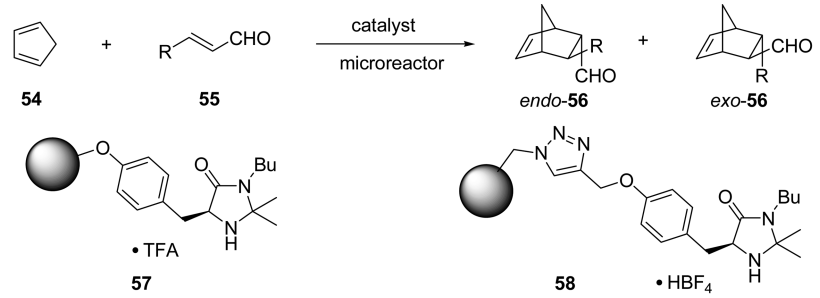
Scheme 24. Schematic Representation of the Experimental Setup for Continuous-Flow α-Aminoxylation of Aldehydes



Scheme 25. Continuous-Flow α-Amination with Azodicarboxylates



Scheme 26. Continuous-Flow Enantioselective Diels–Alder Reaction



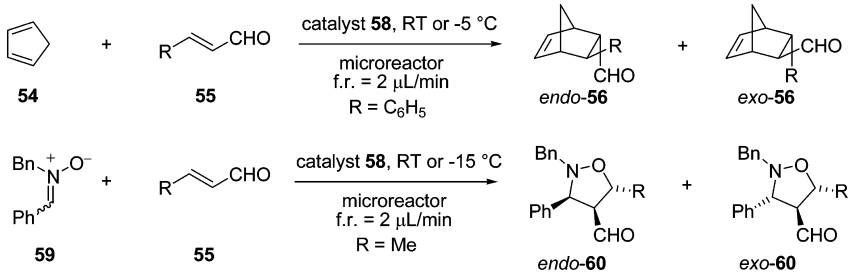
f.r. = 5 μL/min, residence time: 10 h

R = 4-BrC$_6$H$_4$	24h: 44%, 49:51 dr, 81/85% ee 24h: 41%, 48:52 dr, 80/75% ee 12h: washing phase
R = 2-NO$_2$C$_6$H$_4$	14h: 63%, 51:49 dr, 83/75% ee 26h: 55%, 51:49 dr, 81/74% ee 12h: washing phase
R = C$_6$H$_5$	32h: 47%, 53:47 dr, 64/66% ee

f.r. = 2 μL/min, residence time: 12.4 h

R = C$_6$H$_5$	24h: 75%, 47:53 dr, 92/91% ee 8h: washing phase
R = 2-NO$_2$C$_6$H$_4$	16h: 88%, 49:51 dr, 90/91% ee 12h: 55%, 47:53 dr, 91/90 % ee 12h: washing phase
R = Me	14h: 94%, 52:48 dr, 83/75% ee 24h: 47%, 49:51 dr, 85/75% ee 12h: washing phase 30h: 73%, 47:53 dr, 94/89% ee

Scheme 27. Continuous-Flow Cycloaddition Reactions



performed on small as well as larger scale and the desired product **38** was obtained in both cases in good yields and excellent enantioselectivities. Compared to the reaction in batch, a shorter reaction time is required when the transformation is performed under flow conditions (2 vs 8 h).

3.3. Mannich Reactions. Pericàs and co-workers developed heterogeneous catalytic systems for the continuous-flow asymmetric Mannich reactions (Scheme 19 and 20).[40,41] In the first protocol, *syn* Mannich products *syn*-**40** were obtained with excellent enantioselectivities by applying polystyrene resin **41a** functionalized with hydroxyproline as catalyst in a continuous-flow process.[40] With propanal and isovaleraldehyde as aldehyde donors and *N*-PMP protected α-imino ethyl glyoxylate (**7**) as acceptor, the corresponding β-formyl functionalized amino acid derivatives *syn*-**40** were obtained with excellent *syn* diastereoselectivity (97:3 dr) and 99% ee.

A polystyrene-supported pyrrolidine-based catalyst was applied under continuous-flow conditions in order to obtain

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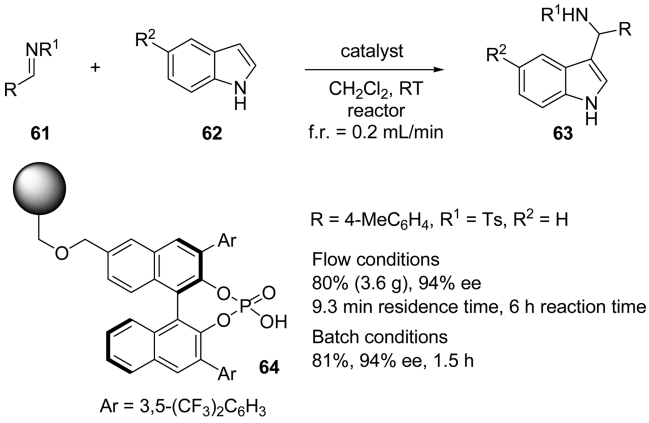
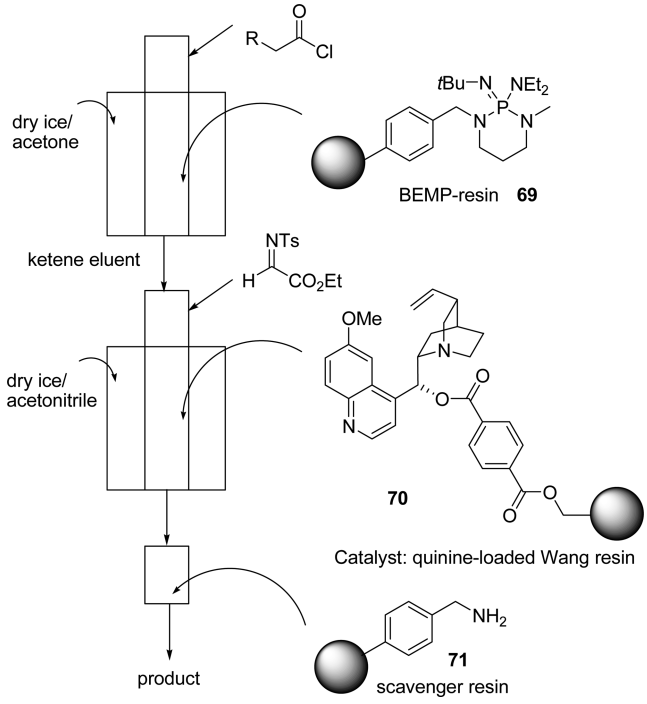
Scheme 28. Continuous-Flow Brønsted Acid-Catalyzed Enantioselective Friedel–Crafts Reaction



Scheme 30. Schematic Representation of the Experimental Setup for the Column-Based-Flow System



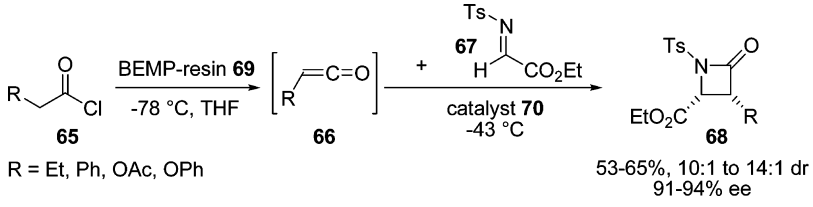
the corresponding anti β-formyl functionalized amino acid derivative products *anti*-**40** (Scheme 20) with excellent diastereoselectivities (89:11 to 95:5 dr) and enantioselectivities (95–97% ee).[41] The reaction was successful also with cyclic ketone derivatives as donors. For example, the reaction between cyclohexanone (**5**) and *N*-PMP protected α-imino ethyl glyoxylate (**9**) delivers the *anti* product (*anti*-**10**) with 81% yield, >95:5 dr and 97% ee. More recently, a heterogeneous enantioselective three-component *anti*-Mannich reaction[42] with a polymer supported threonine-derived catalyst[43] was described under continuous-flow conditions.

The groups of Schneider and Belder performed the Brønsted acid-catalyzed asymmetric vinylogous Mannich reaction in continuous flow by using a microfluidic chip with integrated analysis (Scheme 21).[44] For this purpose, a chip with different incorporated functional areas for performing the reaction, separation by electrophoresis, and mass spectrometric detection was designed. Notably, overall the reaction and MS analysis are extremely fast (3 + 1.5 min). In addition, for the first time, the separation of enantiomers was performed on an additional chip, allowing the rapid determination of enantiomeric excess for the product. The yield of the reaction can be easily determined by using an internal standard. Furthermore, reaction intermediates could be identified with the aid of MS analysis.

3.4. α-Functionalization of Carbonyl Compounds. In 2011, the group of Pericàs described the enantioselective α-aminoxylation of aldehydes in continuous flow with polystyrene-immobilized hydroxyprolines **41b** and **41c** as catalysts in a packed-bed reactor (Scheme 22).[45] Two different cross-linked polystyrenes were used as support for the chiral catalyst. Both final resulting catalysts **41b** and **41c** performed well in the α-aminoxylation of a series of linear and branched aldehydes **30**, providing the corresponding enantiomerically enriched β-aminoxy alcohols **48** (94–98% ee) after reduction. Short residence times are needed (5 min), and the reaction can be performed for several hours, allowing medium-scale preparation of β-aminoxy alcohols. One drawback of the present system is the slow deactivation of the catalyst after 5 h of reaction cycle. From the point of view of productivity, catalyst **41b** containing 1% of the cross-linking agent performed better when compared to catalyst **41c**.

A different reaction setup was devised by McQuade for the proline-catalyzed enantioselective α-aminoxylation of aldehydes. In this case, a cartridge with solid proline was placed before the reaction reactor (Scheme 23).[46] A mixture of solvent, aldehyde, and urea cocatalyst was purged through the column containing the solid proline resulting in a catalytically active species upon releasing the proline and reaction with the aldehyde. The resulting active species (oxazolidinone intermediate) leaves the column and enters the reactor for reacting with nitrosobenzene (Scheme 24). Lastly, reduction of the α-aminoxy aldehydes provides the β-aminoxy alcohols **48** with excellent enantioselectivities (97–99%).

Scheme 29. Continuous-Flow Synthesis of β-Lactams



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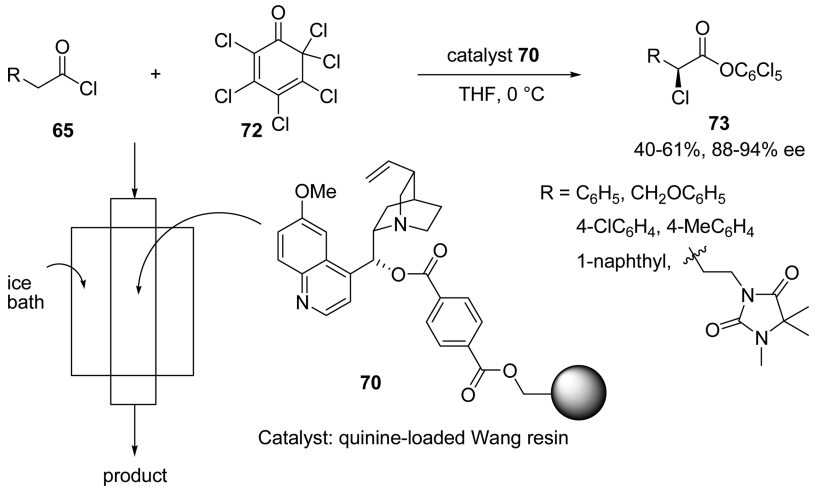
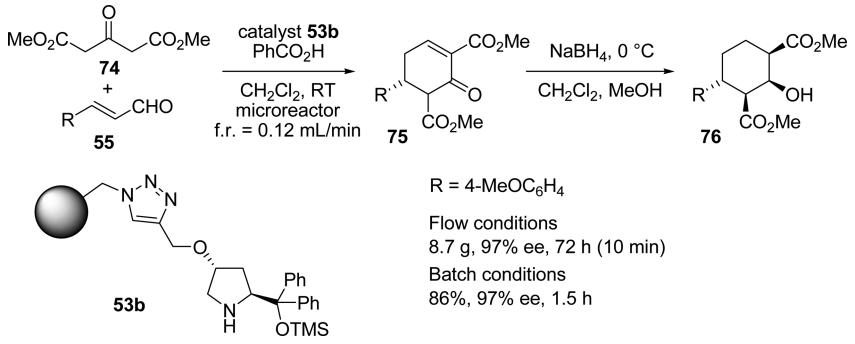
Scheme 31. Continuous-Flow Asymmetric Synthesis of α-Chloroesters



Scheme 32. Continuous-Flow Enantioselective Domino Michael/Knoevenagel Reaction



The asymmetric α-amination of carbonyl compounds has been reported with a variety of organocatalysts. However, the development of robust reusable amine catalysts for this transformation constitutes a challenge for synthetic chemists because the azodicarboxylates applied in these studies react easily with the amine catalysts to the corresponding triazanes. By applying a polystyrene-supported diphenylprolinol silyl ether **53a** as catalyst and using a large excess of aldehyde, the continuous-flow α-amination of propanal was achieved in an efficient manner (6 min residence time, 8 h operation) (Scheme 25).[47]

The α-alkylation of aldehydes was also successfully achieved under continuous-flow conditions with supported chiral imidazolidinone catalysts.[48]

3.5. Cycloaddition Reactions. Cycloadditions reactions are of interest as multiple bonds are formed during one process. Recently, also cycloadditions reactions have been performed in a continuous-flow fashion with silica gel immobilized chiral imidazolidinones as catalysts by the groups of Benaglia and Puglisi.[49,50] For example, the enantioselective Diels–Alder reaction[51] between cyclopentadiene (**54**) and three different aldehydes **55** has been performed with the aid of a HPLC column packed with imidazolidinone **57** (Scheme 26).[49] To show the versatility of the system, the reactions were performed on the same column which was washed with a CH_3CN/H_2O mixture before every new use (Scheme 26 left). More recently, a chiral monolithic reactor containing polymer-supported imidazolidinone catalyst **58** was also described (Scheme 26 right).[50] The same setup was also applied to perform subsequently different types of catalytic reactions. For example, after running the Diels–Alder reaction for 80 h with very high yields (93–99%), poor diastereoselectivity (45:55 to 48:52 dr) and high enantioselectivities (90–91%, 90–93% ee for both diastereomers), the column was washed for 20 h and subsequently used in the [3 + 2]-cycloaddition with moderate yields and high diastereo- and enantioselectivities (91:9 to 94:6 dr, 90% ee for the major diastereomer) (Scheme 27). A final attempt to perform a Friedel–Crafts alkylation of *N*-methyl pyrrole on the same column was less successful as the product was obtained with low yields and enantioselectivities.

3.6. Friedel–Crafts Reaction. Immobilized phosphoric acid catalysts were applied in the continuous-flow enantioselective Friedel–Crafts reaction (Scheme 28).[52] The Brønsted acid-catalyzed enantioselective Friedel–Crafts reaction between indoles and sulfonylimines was previously reported by You and co-workers.[53] Pericàs and co-workers developed a similar protocol for the batch reaction which was extended to efficient catalyst recycling (14 cycles) and continuous flow.[52] The polystyrene-supported BINOL phosphoric acid **64** proved effective in all these transformations. For the continuous-flow reaction of indole (R^2 = H) with 4-tolyl-*N*-tosylmethanimine (R = 4-MeC_6H_4, R^1 = Ts), 3.6 g (9.2 mmol) of the highly enantiomerically enriched product **63** (R = 4-MeC_6H_4, R^1= Ts, R^2 = H) was obtained after 6 h reaction time. Under batch conditions, 0.057 mmol product were obtained after 1.5 h. The same setup can be used to perform subsequent reactions with different indole and imine substrates by employing a washing phase of 30 min with CH_2Cl_2 to clean up the system.

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3.7. Domino Reactions. In 2000, the group of Lectka described the first protocol for performing an organocatalyzed reaction on a column-based-flow system (Schemes 29 and 30).[9] The developed methodology was applied to the synthesis of β-lactams **68** starting from acid chlorides **65** and imines **67**. In fact the whole sequence can be described as a domino reaction consisting of an initial step for the in situ ketene generation which is followed by a catalyzed asymmetric [2 + 2]-cycloaddition reaction.

In 2005, the same group described the asymmetric α-functionalization of carbonyl derivatives with subsequent esterification (Scheme 31).[54] The method is based on a similar column-flow system which takes advantage of the immobilized cinchona alkaloid **70** as catalyst as well as the dehydrohalogenation reagent. In situ generation of the corresponding ketene with subsequent chlorination/esterification allows enantioselective formation of the corresponding α-chloroesters **73** with high enantioselectivities (88−94% ee). The catalyst can be easily regenerated by washing with Hünig's base.

An enantioselective domino Michael/Knoevenagel reaction in continuous flow was described by the group of Pericàs.[55] An immobilized diphenylprolinol silyl ether catalyst **53b** was applied in the continuous-flow reaction between dimethyl 3-oxoglutarate (**74**) and 4-methoxycinnamaldehyde (R = 4-$MeOC_6H_4$) to provide the functionalized cycloheanone derivative **75** which was subsequently reduced to the cyclohexane derivative **76** (Scheme 32). The reaction could be performed continuously for 72 h (10 min residence time) to provide 8.7 g of **76** with 97% ee. This protocol opens new ways for performing organocatalyzed domino reactions, adding a further improvement to the already attractive and established area of metal-free catalyzed domino reactions.

4. CONCLUSIONS

We have summarized and highlighted different advantages associated with organocatalytic transformations performed in continuous-flow systems and presented various types of asymmetric organocatalyzed reactions available to date in continuous flow. As illustrated, these processes have gained a lot of attention in recent years as useful tools for increasing the efficiency of synthetic steps.[56] However, the field of asymmetric organocatalyzed transformations performed in continuous-flow systems is in its infancy and the methods presented are applicable mostly for particular substrates. Examples in which the developed protocols have been tested and perform satisfactory for a larger number of substrates are still rare. Hence, research for developing more generally applicable continuous-flow reactors and robust catalysts is still to be accomplished. In particular, the issues associated with catalyst deactivation have to be overcome. Nevertheless, such processes can tremendously increase the efficiency of the transformations by reducing the reaction time and amount of required catalyst. Therefore, they open up new avenues for large-scale applications, impacting industrial processes.

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Notes

The authors declare no competing financial interest.

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